

### EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Dahna Pasternak on June 19, 2009.

Claims 1-4, 10, 12-15, 17-19 and 23-25 are allowed.

#### ***Claim Amendments***

The application has been amended as follows:

Please cancel claims 11 and 16.

In claim 15, line 2, please delete the phrase "or a fragment thereof".

2. Claims 1-4, 19, 23 and 25 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 10-14, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104. Additionally, the former species requirement was withdrawn during the prosecution of this application and non-elected claims 15, 17, 18 and 24 have been rejoined and are allowed.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on 9/26/06 is hereby withdrawn.** In view of the withdrawal of the restriction

requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

3. The following is an examiner's statement of reasons for allowance:

The cited prior art fails to provide evidence that a mutated CT-A or LT-A protein comprising the combined substitutions at the position corresponding to Ser-63-Lys and the position corresponding to Arg-192-Asn/Gly would not only retain immunogenicity, but also be detoxified.

In the instant case, the combination of references does not teach or suggest that the claimed double mutants were predictable in terms of being detoxified and/or immunogenic. None of the references actually show that the claimed double mutants are both detoxified and immunogenic, let alone show that the claimed molecules are predictable as required to show obviousness. Domenighini teaches that mutating the Arg192 residue does not result in reduced toxicity. See, Table I, row O of Domenighini on page 46 of the reference. Simply put, Domenighini does not teach anything predictable about double mutants generally, and teaches away from the specifically claimed detoxified double mutant.

Pizza also fails to teach anything about double mutants as claimed. Pizza does not teach that mutating position Arg192 decreases the rate of proteolysis. Rather, like Domenighini, Pizza teaches away from mutating the Arg192 residue to reduce proteolysis and/or toxicity (see, page 57, right column of Pizza, emphasis added):

*Arg-192.* Arg-192 is part of the surface exposed loop ... that needs to be cleaved at the Arg residue in order to allow entrance of the A1 domain into the cell membrane and cause toxicity (Spicer and Noble, 1982). Substitution with a polar amino acid (Asn) was designed to introduce a residue still surface-exposed but resistant to proteolysis. Unexpectedly, the mutant LT was found to be fully toxic, suggest[ing] either that the substitutions did affect proteolysis at all, or that the rate of proteolysis was only decreased to a level that did not affect toxicity in vivo.

Thus, Pizza teaches nothing about double mutants and teaches away from mutating the Arg-192 residue inasmuch as the Arg192Asn mutation had no effect on toxicity. Finally, Clements also fails to establish anything about the predictable use of double mutants, as claimed. Clements discloses one mutant only and gives no indication that double mutants would be either functional or in any way desirable. Furthermore, given that Domenighini and Pizza both clearly teach that their Arg192 mutations do not detoxify the protein, the combination of cited references does not establish predictability of this single mutant, let alone the claimed double mutants.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/  
Primary Examiner, Art Unit 1645

6/19/09